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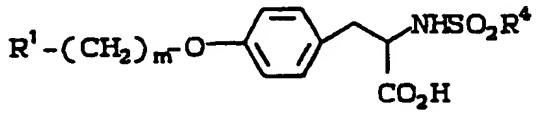
(54) Title: PROCESS FOR THE PREPARATION OF 0-[4-(4-PIPERIDINYL)BUTYL]-TYROSINE DERIVATIVES AS FIBRINOGEN RECEPTOR ANTAGONISTS



(I)

(57) Abstract

The invention is a highly efficient synthesis for making compounds of formula (I), wherein R^1 is a six member saturated or unsaturated heterocyclic ring containing ne or two heteroat ms wherein the heteroatoms are N; or NR^6, wherein R^6 is H or C_{1-10} alkyl; m is an integer from two to six; and R^4 is aryl, C_{1-10} alkyl, or C_{4-10} aralkyl.

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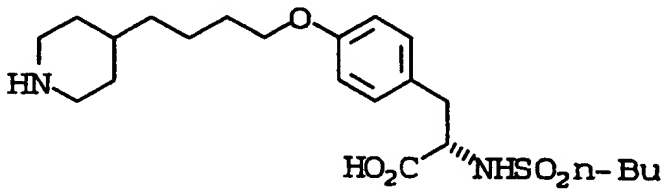
TITLE OF THE INVENTION - 1 -

PROCESS FOR THE PREPARATION OF O-[4-(4-PIPERIDINYL)BUTYL]-TYROSINE DERIVATIVES AS FIBRINOGEN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

United States Serial No. 750,647, filed August 30, 1991, describes fibrinogen receptor antagonists, and procedures for preparing fibrinogen receptor antagonists, which are prepared according to the procedure of the present invention. In particular, the compound:



is prepared according to an 11-step procedure involving the formation of potentially hazardous NaH/DMF for ether formation, which required a chromatographic purification.

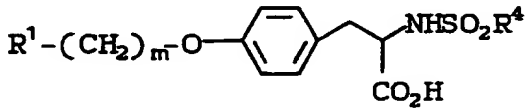
Zenitz, U.S. Patent 3,124,586 and Singerman et al., J. Heterocyclic Chem. (1966), 3, 74, describe a procedure for preparing 4-(4-pyridinyl)butanol.

Beumel et al., Synthesis (1974), 43; Screttas et al., Chimia (1970), 109; and Osuch et al., Chimia (1956), 1723, describe a procedure for metallation of 4-picoline.

Barlos et al., Liebigs. Ann. Chem. (1986), 1407 describe Mitsunobu alkylation of tyrosine derivatives.

SUMMARY OF THE INVENTION

The invention is a highly efficient synthesis for making compounds of the formula:



wherein:

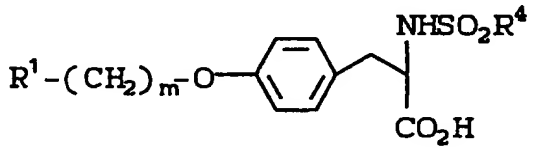
R^1 is a six member saturated or unsaturated heterocyclic ring containing one or two heteroatoms wherein the heteroatoms are N; or NR^6, wherein R^6 is H or C_{1-10} alkyl;

m is an integer from two to six; and

R^4 is aryl, C_{1-10} alkyl, or C_{4-10} aralkyl.

DETAILED DESCRIPTION OF THE INVENTION

The invention is a process for preparing fibrinogen receptor antagonists of the formula:



wherein

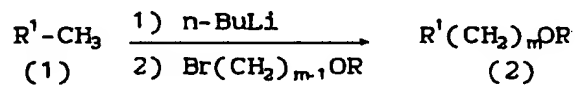
R^1 is a six member saturated or unsaturated heterocyclic ring containing one or two heteroatoms wherein the hetero atoms are N; or NR^6 wherein R^6 is C_{1-10} alkyl;

m is an integer from two to six; and

R^4 is aryl, C_{1-10} alkyl, or C_{4-10} aralkyl,

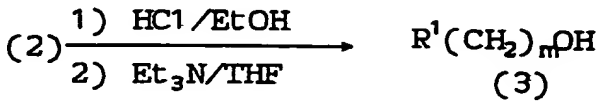
according to the procedure whereby

1)



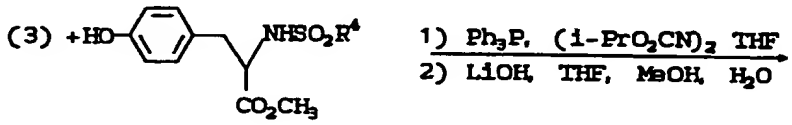
methylated R^1 is reacted with nBuLi, before quenching with a straight chain alkyl group having Br at one end and OR at the other end, to yield (2), wherein R is tetrahydropyran;

2)

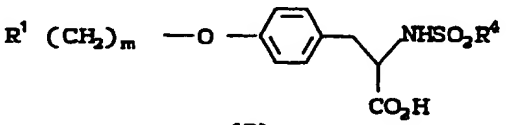


(2) is aged, first in hydrogen chloride gas in ethanol, and then neutralized in triethylamine/tetrahydrofuran, to form (3); and

3)



(4)

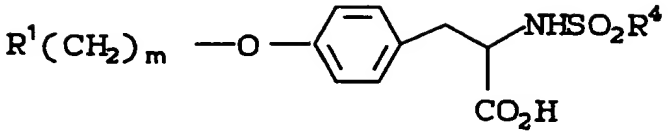


(5)

(3) is combined with (4) to yield (5) after ester hydrolysis.

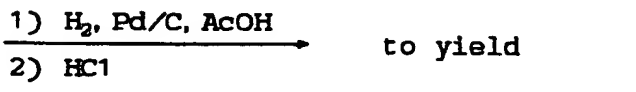
Preferably, when

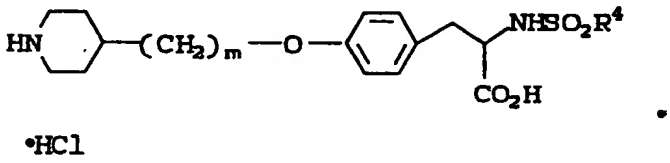
R^1 is pyridine,



(5)

is selectively hydrogenated using Pd/C in acetic acid

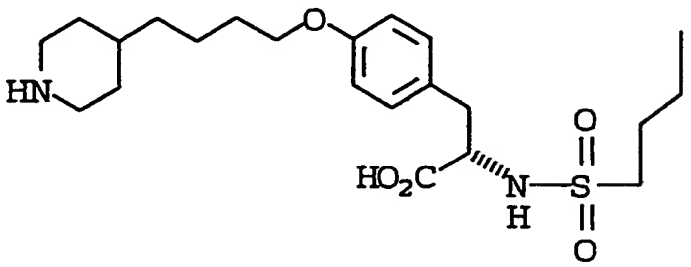




•HCl

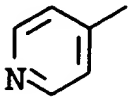
The synthesis of the invention uses inexpensive starting materials, and employs the Mitsunobu reaction to effect the ether formation in high yield and simple purification procedure. The prior art reaction employs a potentially hazardous NaH/DMF mixture to effect the ether formation in low yield, which required a chromatographic purification.

Preferably, the invention is a highly efficient synthesis for making

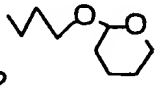


The six-step synthesis employs 4-picoline, as a latent form of piperidine, which eliminates the need for protection. O-alkylation of a tyrosine derivative under Mitsunobu condition followed by saponification of the methyl ester, extractive removal of the Mitsunobu by-products, and recrystallizations provide the coupled product in high yield and purity. Selective hydrogenation of the pyridine ring is achieved by using 10% Pd/C in AcOH at 70°C.

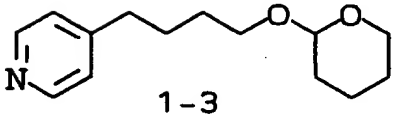
EXAMPLE 1



1-1

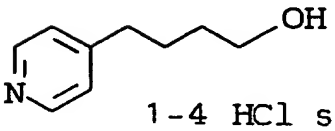
1) n-BuLi
2) Br 

1-2



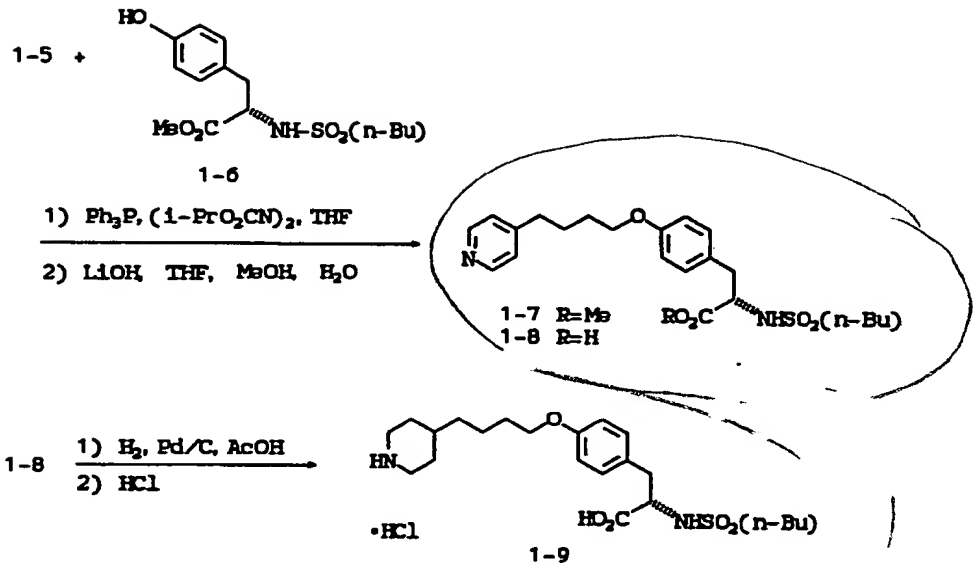
1-3

1) HCl/EtOH
2) Et_3N/THF



1-4 HCl salt

1-5 free base


1-5 +
HO
MeO2C
NH-SO2(n-Bu)
1-6
1) Ph3P, (i-PrO2CN)2, THF
2) LiOH, THF, MeOH, H2O
1-7 R=Me
1-8 R=H
RO2C
NHSO2(n-Bu)
1-8
1) H2, Pd/C, AcOH
2) HCl
HN
•HCl
HO2C
NHSO2(n-Bu)
1-9

103

Preparation of N-n-Butanesulfonyl-(L)-tyrosine methyl ester (1-6)

A 50 L four-neck round bottom flask equipped with a mechanical stirrer, condenser, nitrogen inlet, HCl trap, heating unit and a thermometer probe was purged with nitrogen overnight and then charged with (L)-tyrosine methyl ester HCl salt (1304 g, 5.628 mol), CH_3CN (16 L), pyridine (994.3 g, 12.57 mol) and n-butanesulfonyl chloride (924.83 g, 5.906 mol). The mixture was heated at 65°C for 20 h. The solvent was removed in a batch concentrator under house vacuum at 40°C over 1-2 days. The resulting black oil was washed with 10% $KHSO_4$ (8.5 L) and the mixture extracted with methylene chloride (4 x 8 L). The organic was filtered through 2.9 kg $MgSO_4$ (top) and 1.3 kg flash-grade SiO_2 (bottom) in a sinter glass funnel. Evaporation of the filtrate gave ~1021 g solid (purity = 90 A%). The solid was dissolved in toluene (5L) with heating and the batch was aged at ambient temperature for 5 h and then filtered. The filter cake was washed with toluene (2L) and dried to give 857.5 g (48%) of 1-6 as an off-white solid. mp 70-71°C; $[\alpha]^{25}_D$ = -27.0° (c 0.967, MeOH); MS(EI) m/z 315 (M+).

^1H NMR (CD_3OD) δ 7.06 (d, J = 7.7 Hz, 2H), 6.72 (d, J = 7.7 Hz), 4.10 (ABq, J = 9.6, 5.1 Hz, 1H), 3.02 (ABq, J = 13.7, 5.1 Hz, 1H), 2.73 (ABq, J = 13.7, 9.6 Hz, 1H), 2.61 (t, J = 7.9 Hz, 2H), 1.41 (m, 2H), 1.33 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H).

^{13}C NMR (CD_3OD) δ 174.1, 157.6, 131.6, 128.8, 116.3, 59.5, 54.1, 52.8, 39.0, 26.5, 22.5, 13.9. Anal. Calcd for $C_{14}H_{21}O_5NS$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.37; H, 6.86; N, 4.42.

Preparation of 4-(4-Pyridinyl)butanol (1-5)

A 12 L four-neck round bottom flask equipped with a mechanical stirrer, condenser, addition funnel with side-arm and a thermometer probe was purged with nitrogen overnight. THF (2.4 L) and 4-picoline (322.5 g, 3.46 mol) were added and the batch was cooled to -40°C. A solution of n-butyllithium (2.69 L of 1.56 M solution, 4.21 mol) in hexane was added slowly while keeping the internal temperature ≤-30°C. The addition took about 1 h to give an orange solution with some precipitate. The batch was warmed to ambient temperature, aged for four hours and then cooled to -20°C. A solution of 2-(3-bromopropyloxy)-tetrahydropyan (850.0 g, 3.81 mol) in dry THF (450 mL) was added slowly via an addition funnel, maintaining the batch temperature at ≤-5°C, and then the batch was aged at ambient temperature overnight. Ice water (3 L) was added and the mixture was extracted with ethyl acetate (1 x 2 L, 1 x 1.5 L, 1 x 1 L). The combined organic layers were washed with water (4 L) and then concentrated to give ~874 g of crude 1-3 as an oil, which is used directly in the next step.

To a solution of crude 1-3 (873 g) in ethanol (3.5 L) was added a solution of HCl gas (278 g, 7.61 mol) in ethanol (2.5 L). The mixture was stirred at ambient temperature for 3 h, then concentrated under vacuum. The resulting oil was dissolved in warm isopropanol (700 mL) and ethanol (50 mL), then with mechanical stirring isopropyl acetate (1.2 L) was added slowly. The mixture was aged for 18 h at ambient temperature, cooled (with

ice water) and filtered under nitrogen. The filter cake was washed with isopropyl acetate (3 x 500 mL) and vacuum-dried under nitrogen to give ~280 g of 1-4.

To a mixture of compound 1-4 (280 g) in dry THF (2 L) was added slowly a solution of triethylamine (166 g, 1.64 mol) in THF (400 mL). The mixture was stirred for 2 h, filtered and the filter cake (triethylamine hydrochloride) was washed with THF (2 x 500 mL). The filtrate was evaporated to dryness under vacuum to give 200 g compound 1-5 in 40% overall yield from 4-picoline.

1-4: mp 153-154°C; MS(CI) m/z 151 (M^+ - HCl).
^1H NMR (CD_3OD) δ 1.63 (m, 2H), 1.89 (m, 2H), 2.99 (t, J = 7.8 Hz, 2H), 3.60 (t, J = 6.2 Hz, 2H), 7.98 (d, J = 6.5 Hz, 2H), 8.72 (d, J = 6.5 Hz, 2H);
^{13}C NMR (CD_3OD) δ 27.3, 32.9, 36.7, 62.2, 128.6, 142.1, 166.6.
Anal. Calcd for $C_9H_{14}NOCl$: C, 57.60; H, 7.52; N, 7.46; Cl, 18.89. Found: C, 57.65; H, 7.34; N, 7.33; Cl, 19.17.

Preparation of N-(n-Butanesulfonyl)-O-(4-(4-pyridinyl)butyl)-(L)-tyrosine (1-8)

To a dry 5 L three-neck round bottom flask equipped with a mechanical stirrer, nitrogen inlet and a thermometer probe containing a solution of N-n-butanesulfonyl-(L)-tyrosine methyl ester (400.3 g, 1.268 mol) and triphenylphosphine (417.5 g, 1.595 mol) in THF (600 mL) was slowly added a solution of 4-(4-pyridinyl)-butanol (207.0 g, 1.37 mol) and diisopropyl azodicarboxylate (319.9 g, 1.582 mol) in

THF (475 mL) via a 1-L addition funnel over 3.5 h. The temperature was maintained at 23-26°C using a water bath. The mixture was allowed to stir for additional 30 min, then hexane (1.1 L) and methylene chloride (60 mL) were added. The resulting mixture was loaded onto sand (1 kg, on top)/Silica Gel 60 (3 kg) in a 5 L sintered glass funnel, eluted with 1:1 hexanes/THF (32 L), and collected 2-L fractions. Fractions 1-8 were combined and the precipitate Ph_3PO was filtered. The filter cake was washed with 1:1 hexanes/THF (300 mL). The filtrate was concentrated to give 1051 g of crude methyl ester 1-7 as an oil.

To a solution of 1-7 (1051 g) in THF/MeOH/H_2O (3:1:1, 5 L) was added slowly solid $LiOH \cdot H_2O$ (108.5 g, 2.58 mol) at 25-29°C over 30 min. The mixture was aged for 1.5 h and then quenched by adding DI water (4 L) and conc. HCl (125 mL) to give a final pH 10.4. The mixture was diluted with water (4 L) and extracted with isopropyl acetate (4 x 3 L) and the combined organic layer was back-extracted with 0.1 N NaOH (3 L). The combined aqueous layer was acidified to pH 4.5 using conc. HCl (100 mL) and then extracted with methylene chloride (3 x 4 L). The methylene chloride extracts were filtered through sand (1 kg, on top)/ Silica Gel 60 (3 kg) in a 5 L sintered glass funnel, then eluted with ethyl acetate (4 L), ethyl acetate/ methanol/acetic acid (12 L/0.6 L/60 mL) and ethyl acetate/methanol/acetic acid (28.1 L/3.5 L/350 mL), and collected in 4-L fractions. The product-enriched fractions 4-8 were combined and evaporated to dryness to give 466 g wet solid. The solid was recrystallized

from isopropyl alcohol (6 L) by warming to 50°C first and then cooling slowly to ambient temperature with stirring overnight. The slurry was filtered, washed with isopropyl alcohol (2 x 200 mL) and air-dried to give 305 g (55%) of 1-8.

HPLC Assay: product 1-8, 99.5% area; RT = 6.76 min; Zorbax RX-C8 column, 4.6 mm x 25 cm ID; 220 nm; 1.5 mL/min; linear gradient 10 to 90% A over 10 min, A = CH_3CN, B = 0.1% aqueous H_3PO_4.

mp 137-138°C; $[\alpha]^{25}_D$=-14.7° (c 0.91, MeOH); MS(CI) m/z 435 (MH^+).

^{1}H-NMR (CD_3OD) δ 0.86 (t, J=7.3Hz, 3H), 1.33 (hex, J=7.3Hz, 2H), 1.68 (m, 2H), 1.83 (m, 2H), 2.82 (m, 2H), 3.06 (A of ABX, J_{AB}=13.9Hz, J_{AX}=6.3Hz, 1H), 3.16 (B of ABS, J_{BA}=13.9Hz, J_{BX}=5.0Hz, 1H), 3.90 (t, J=5.7Hz, 2H), 4.32 (X of ABX, J_{XA}=6.3Hz, J_{XB}=5.0Hz, 1H), 6.72 (d, J=8.6Hz, 2H), 7.17 (d, J=8.6Hz, 2H), 7.33 (d, J=6.3Hz, 2H), 8.49 (d, J=6.3Hz, 2H);

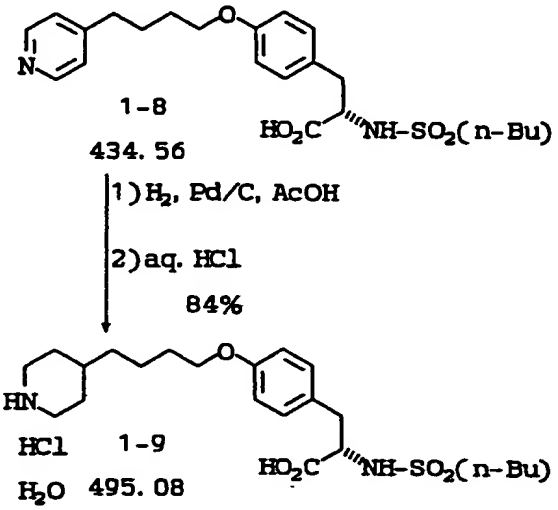
^{13}C-NMR ($CDCl_3$) δ 13.5, 21.5, 25.4, 26.5, 28.6, 35.1, 38.9, 53.0, 57.9, 67.0, 114.3, 125.0, 128.7, 130.8, 145.9, 155.8, 157.7, 175.0;

Anal. Calcd for $C_{22}H_{30}O_5SN_2$:

C, 60.81; H, 6.96; N, 6.45; S, 7.38.

Found: C, 60.53; H, 6.88; N, 6.26; S, 7.65.

Preparation of N-(n-butanesulfonyl)-O-(4-(4-piperidinyl)butyl)-(L)-tyrosine, hydrochloride, monohydrate (1-9)



Pyridine 1-8 (274.6 g, 0.632 mol) and 10% Pd/C (27.5 g, 10 wt%) in acetic acid (2.75 L) was hydrogenated in a stainless steel vessel at 40 psi and 70°C until complete uptake of hydrogen was observed (4-6 h). The reaction mixture was filtered through a pad of Solka-Flock (280 g; prewashed with 1 L acetic acid) and then washed with acetic acid (1 L). The filtrate was concentrated to a thick oil containing approximately 285 g acetic acid, then DI water (4.125 L) was added to give a concentration of 1 g/15 mL 7% acetic acid in water and the resulting slurry was stirred at 50°C for 1 hour and at ambient temperature for 18 hours. The solid was collected on

a sintered glass funnel, washed with DI water (3 x 350 mL) and dried under vacuum with nitrogen sweep to give 238.4 g (86%) of free base of 1-9 as a white solid.

HPLC Assay: free base of 1-9, 99.5 area %, RT=6.94 min; Zorbax RX-C8 column, 4.6 mm x 25 cm ID; 220 nm; 1.5 mL/min; linear gradient 20 to 70% A over 12 min, A=CH_3CN, B=0.1% aqueous H_3PO_4. mp 223-225°C; $[\alpha]^{25}_D$= -14.7° (c 0.91, MeOH).

^{1}H-NMR (CD_3OD) δ 0.88 (t, J=7.3Hz, 3H), 1.33 (m, 6H), 1.58 (m, 5H), 1.76 (m, 2H), 1.81 (m, 2H), 2.77 (t, J=7.5, 2H), 2.80 (m, 1H), 2.88 (m, 2H), 3.03 (B of ABX, J_{BA}=13.9Hz, J_{BX}=4.6Hz, 1H), 3.30 (m, 2H), 3.90-4.0 (m, 3H), 6.80 (d, J=8.5Hz, 2H), 7.18 (d, J=8.5Hz, 2H). Anal. Calcd for $C_{22}H_{37}O_5N_2S$:
C, 59.84; H, 8.40; N, 6.34; S, 7.24.
Found: C, 59.98; H, 8.40; N, 6.40; S, 7.24.

To a rapidly stirred suspension of free base of 1-9 (24.64 g, 55.93 mol) and isopropyl acetate (1 L) was added concentrated hydrochloric acid (10 mL) dropwise. The temperature remained at 19°C throughout addition. The mixture was then stirred at room temperature (19°C) for a further 6 hours. The product was isolated by filtration under nitrogen. The solid product was washed with isopropyl acetate (2x100 mL) and suction-dried under nitrogen overnight to afford 27.1 g (98%) of 1-9.

HPLC Assay: 1-9, 99.8 area%; RT=6.79 min; Zorbax RX-C8 column, 4.6 mm x 25 cm ID; 220 nm; 1.5 mL/min;

linear gradient 10 to 90% A over 10 min, A=CH_3CN, B=0.1% aqueous H_3PO_4; or 1-9, 99.8 area%, RT=6.94 min; Zorbax RX-C8 column, 4.6 mm x 25 cm ID; 220 nm; 1.5 mL/min; linear gradient 20 to 70% A over 12 min, A=CH_3CN, B=0.1% aqueous H_3PO_4.

Chiral HPLC: L-isomer, >99.9%; RT=10 min; D-isomer, <0.1%; RT=8.5 min; ULTRON-ES-OVM column, 4.6 mm x 25 cm, 5 m, with guard column; 270 nm; 0.7 mL/min; isocratic, 90% Buffer (6 g ammonium formate adjusted to pH 4.1 with formic acid), 10% MeOH. mp1 87-88°C, mp2 131-132°C; $[\alpha]^{25}_D$=-14.4° (c 0.92, MeOH);

^{1}H-NMR (CD_3OD) δ 0.84 (t, J=7.3Hz, 3H), 1.23 (hex, J=7.3Hz, 2H), 1.30-1.70 (m, 9H), 1.75 (m, 2H), 1.95 (m, 2H), 2.64 (t, J=7.4, 2H), 2.77 (A of ABX, J_{AB}=13.9Hz, J_{AX}=9.8Hz, 1H), 2.95 (m, 2H), 3.11 (B of ABX, J_{BA}=13.9Hz, J_{BX}=4.6Hz, 1H), 3.47 (m, 2H), 3.95 (t, J=6.2Hz, 2H), 4.09 (X of ABX, J_{XA}=9.8Hz, J_{XB}=4.6Hz, 1H), 6.84 (d, J=8.6Hz, 2H), 7.18 (d, J=8.6Hz, 2H).

^{13}C-NMR (CD_3OD) δ 14.0, 22.5, 24.0, 26.5, 30.0, 30.4, 34.8, 36.8, 39.0, 45.3, 54.1, 59.4, 68.7, 115.5, 130.4, 131.7, 159.6, 175.2.

IR (Nujol, cm^{-1}) 3520, 3208, 3166, 2800-2300, 1727, 1610, 1595, 1324, 1256, 1141, 1119, 829.

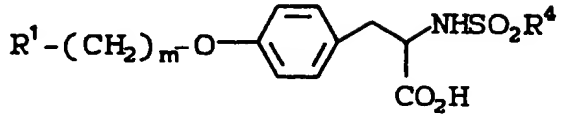
HRMS calcd for $C_{22}H_{37}N_2O_5S$ 441.2423, found 441.2423 (M^+-H_2O-HCl). Anal. Calcd for $C_{22}H_{39}O_6ClN_2S$:

C, 53.37; H, 7.94; N, 5.66; Cl, 7.16; S, 6.48.

Found: C, 53.56; H, 8.04; N, 5.62; Cl, 7.36; S, 6.53.

WHAT IS CLAIMED IS:

1. A process for preparing compounds of the following formula:



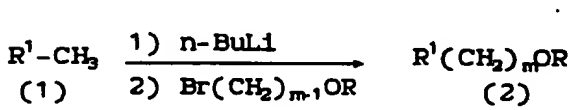
wherein:

R^1 is a six member saturated or unsaturated heterocyclic ring containing one or two heteroatoms wherein the heteroatoms are N; or NR^6, wherein R^6 is C_{1-10} alkyl;

m is an integer from two to six; and

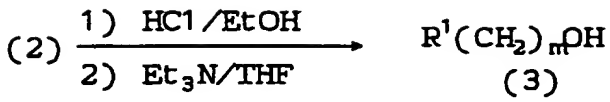
R^4 is aryl, C_{1-10} alkyl, or C_{4-10} aralkyl,

according to the process steps whereby



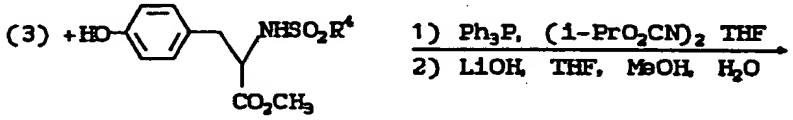
methylated R^1 is reacted with nBuLi, before quenching with a straight chain alkyl group having Br at one end and OR at the other end, to yield (2), wherein R is tetrahydropyran;

2)

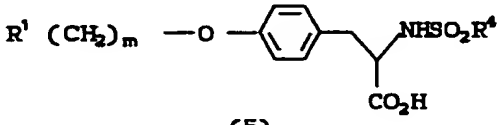


(2) is aged, first in hydrogen chloride gas in ethanol, and then neutralized in triethylamine/tetrahydrofuran and to yield (3); and

3)



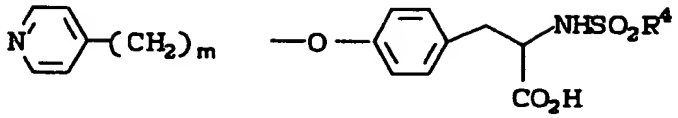
(4)



(5)

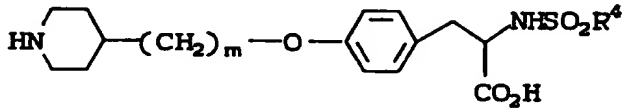
(3) is combined with (4) to yield (5).

2. A process according to Claim 1, wherein R^1 is pyridine, and



(5)

is selectively hydrogenated using Pd/C in acetic acid to yield



INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/01621

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D211/22; C07D213/30

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A,P	EP,A,0 478 363 (MERCK) 1 April 1992 cited in the application see page 10 - page 13 & US910 750 647 30 August 1991	1-2
A	US,A,3 412 138 (SOLAR ET. AL.) 19 November 1968 see the whole document	1-2

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 APRIL 1993	13. 05. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Bernd Kissler

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. vol. 78, no. 8, 1956, GASTON, PA US pages 1723 - 1725 C. OSUCH, R. LEVINE 'The Use of Organlithium Compounds to effect Alkylation of 2- and 4-Picoline.' cited in the application * see page 1724, right column and experimental section *	1-2
Y	SYNTHESIS 1974, STUTTGART DE pages 43 - 45 cited in the application see the whole document	1-2
Y	JUSTUS LIEBIGS ANNALEN DER CHEMIE. 1986, WEINHEIM DE pages 1407 - 1412 BARLOS ET. AL. 'Redox-Alkylierung von Tyrosin-Derivaten.' cited in the application see page 1407 - page 1408	1-2
Y	SYNTHESIS 1981, STUTTGART DE pages 1 - 28 O. MITSUNOBU 'The Use of Diethyl Azodicarbonate and Triphenylphosphine in Synthesis and Transformation of Natural Products.' see the whole document	1-2
Y	CHEMICAL ABSTRACTS, vol. 102, 1985, Columbus, Ohio, US; abstract no. 166849, see abstract & AUST. J. CHEM. vol. 37, no. 12, 1984, pages 2447 - 2451	1-2
Y	J. HET. CHEM. vol. 3, 1966, pages 74 - 78 G. M. SINGERMAN ET. AL. 'Synthesis of Alkylaminoethanethiolsulfuric Acids Substituted with Heterocyclic Moieties' cited in the application * see page 76,78; Ex. XXI *	1-2

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	CHIMIA vol. 24, 1970, SCRETTAS ET. AL. 'Selective Side Chain Alkylation of Toluene and Methylpyridines.' cited in the application see the whole document	1-2

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9301621
SA 71108

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0478363	01-04-92	AU-A- 8478291	02-04-92
		CA-A- 2052073	28-03-92
		JP-A- 4288051	13-10-92
US-A-3412138		None	

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82